REMARKS

Applicants have amended Claims 1, 4 and 33. Claims 1-33 are now pending, of which Claims 5-25 and 27-32 are withdrawn. Claim 1 has been amended to include an additional limitation, and the term "substituted phenyl" has also been deleted from Claim 1. Claim 4 has been amended to simplify or clarify the claim language. Claim 33 has been amended to add 'and' before recitation of the last compound in the Markush group to overcome the rejection.

Rejections Under 35 U.S.C. §112, first paragraph

The Examiner rejected Claims 1-4 and 26 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner contended that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention based on the *Wands* factors.

With regard to treating or preventing an allergic reaction associated with increased IgE levels and asthma, Applicants' disclosure is sufficient to enable those skilled in the art to make and use the invention without undue experimentation. First, the recited pharmaceutical compositions are limited to those for treating or preventing allergic reactions that are associated with an increase in IgE levels and not any and all allergic reactions regardless of their etiology. Second, Applicants have amply demonstrated that the disclosed compounds are effective in both suppressing IgE response and lowering antigen-induced increases in IgE concentration *ex vivo* and *in vivo* (see e.g., Example 2). Third, it was well known to those skilled in the art of allergy treatment that certain allergic reactions are caused by an increased in IgE levels that can lead to various allergy symptoms, and that reducing the IgE concentration or suppressing IgE response could be useful in treating and preventing those allergic reactions associated with an increase in IgE levels.

The role of IgE in allergy was discovered as early as 1970 (see ref. (6) below). To exemplify what was and is well known to those skilled in the art of allergy treatment, copies of the following references are attached:

(1) Sutton, B.J. and Gould, H.J. The human IgE network. *Nature* **366**, 421-428 (1993);
(2) Gauchat, J. et al. Induction of human IgE synthesis in B cells by mast cells and basophils. *Nature* **365**, 340-343 (1993).
(3) http://www.worldallergy.org/professional/allergic_diseases_center/ige/; and
(4) http://www.clevelandclinic.org/health/health-info/docs/1900/1948.asp?index=8610.

(5) Sicherer, S.H., M.D., Manifestations of Food Allergy: Evaluation and Management, *American Family Physician*, Jan. 15, 1999.
(6) Jardieu P.M. and Fick R.B. Jr., IgE inhibition as a therapy for allergic disease, *Int Arch Allergy Immunol.* **118**, 112-115 (1999).
(7) Patalano, P., Injection of anti-IgE antibodies will suppress IgE and allergic symptom, *Allergy* **54**, 103-110 (1999).

Ref. (1) teaches that allergy is generally caused by the overproduction of IgE in response to common environmental antigens, and that IgE is a target for therapeutic intervention. This shows that the common understanding in the field is that an increase in IgE level causes most allergies. Ref. (2) teaches that the IgE is central to the induction of allergic diseases through its binding to a receptor on mast cells and basophils, and thus also demonstrates the common understanding of such concept in the field. Ref. (3) teaches the general mechanism of allergic reactions, and that the corresponding IgE antibodies of an allergen are produced when an allergy-prong person is exposed to an allergen. Furthermore, the IgE antibodies cause the mast cells to release inflammatory chemicals, histamine and/or other chemicals that lead to various allergic reactions. Ref. (4) also teaches the role of IgE in the mechanism of allergic reactions. In addition, it states that "[n]ew pharmacotherapy in the form of a humanized monoclonal anti-IgE antibody designed to eliminate IgE may have a valuable role in treating IgE sensitized individuals." Ref. (5) also points out that the symptoms of IgE-mediated reactions may involve the skin, respiratory system and gastrointestinal track. Ref. (6) and (7) indicate that eliminating serum IgE can be used as a novel treatment for allergic disease, as both articles describe using anti-IgE antibodies to eliminate IgE for treating allergies. This shows that a skilled artisan would understand and appreciate that lowering IgE concentration or inhibiting IgE response would be useful for treating allergic reactions caused by an increase in IgE levels. Furthermore, a skilled artisan would also understand that a variety of allergic reactions may be treated using the claimed compounds as long as the allergic reaction is caused by an increase in IgE levels. Given what is well known in the field, Applicants' disclosure in the specification has enabled those skilled in the art to make and use the invention.

Applicants also respectfully disagree that undue experimentation is needed to practice the method for treating an allergic reaction associated with an increase in IgE levels. Applicants disclosed results of both *ex vivo* and *in vivo* testing of a large number of claimed compounds, therefore have provided sufficient working examples to show the effectiveness of claimed genera

in inhibiting IgE response and lowering IgE levels in mammals. A skilled artisan would logically connect lowering IgE levels with treating an allergic reaction associated with an increase in IgE levels, and could select a group of claimed compounds for more comprehensive clinical testing. "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The state at which an invention in this field becomes useful is well before it is ready to be administered to human." *In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995). The test results (including both *ex vivo* and *in vivo*) as a whole were sufficient to establish pharmacological activity for treating asthma and an allergic reaction associated with an increase in IgE levels in the minds of those skilled in the art. The additional experimentation involves routine screening for skilled artisans in the field of allergy treatment and is reasonable experimentation under patent law.

Thus, Applicants have defined the scope of the claimed invention as being limited to asthma and allergic reactions that are caused by increased IgE levels, Applicants have provided an enabling disclosure for pharmaceutical compositions that are useful in treating or preventing such allergic reactions by demonstrating that the recited compounds reduce IgE levels (scope of enablement commensurate with scope of claims), and Applicants respectfully point out that one skilled in the art either knows (as is well known in the field), or can readily determine with reference to the literature, which allergic reactions are implicated within the scope of Claim 1 – without undue experimentation.

Applicants have further amended Claim 1 to add the limitation "NF-κB-mediated cellular proliferation." The specification discloses the *in vitro* test results on the anti-proliferation effects of compounds of preferred embodiments on a battery of tumor lines with proliferation driven by NF-κB (Example 3). The dosage range for treating NF-κB-mediated cellular proliferation has also been provided in Example 3 of the specification. Similarly, the additional experimentation involves routine screening by skilled artisans in the field of anti-proliferation treatments and is reasonable experimentation under patent law. Applicants' disclosure is also sufficient to enable those skilled in the art to make and use the pharmaceutical composition for inhibiting NF-κB-mediated cellular proliferation without undue experimentation. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-4 and 26.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected Claim 33 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants have amended Claim 33 to add an "and" before the last compound listed in the claim. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-4 and 26.

Rejections Under 35 U.S.C. §102(b)

The Examiner rejected Claims 1-3 and 26 under 35 U.S.C. §102(b) as being anticipated by Masukawa et al. (CA 111:31259 (1989)) because it discloses a compound (CA Registry No. 121216-46-4) that is embraced by the instant claimed invention. Applicants have further amended Claim 1 to exclude the disclosed compound by deleting "substituted phenyl" from the group that R′ is to be selected from. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3 and 26.

Rejections Under 35 U.S.C. §103(a)

The Examiner maintained the rejection of Claims 1-3 and 26 under 35 U.S.C. §103(a) as being unpatentable over Masukawa et al. (U.S. Patent 5,017,468) and Ninomiya et al. (EP 353,606). The Examiner cited *In re Dillon* and argued that there is no requirement that the prior art must suggest that the claimed product will have the same or similar utility as that discovered by applicant in order to support a legal conclusion of obviousness.

Applicants respectfully submit that the Examiner has not shown that the present claims are *prima facie* obvious over the cited prior art. The *prima facie* obviousness finding requires that (1) there must be some suggestion or motivation to modify the prior art reference, (2) there must be a reasonable expectation of success and (3) the prior art reference must teach or suggest all claim limitations. M.P.E.P. 2143. Based on *Dillon*, the Examiner may have shown that there is enough suggestion in the prior art to modify either Masukawa or Ninomiya to arrive at compounds claimed in the present application. However, Applicants submit that the cited prior art references fail to teach or suggest all claim limitations. Applicants are claiming a pharmaceutical composition for treating or preventing an allergic reaction associated with

increased IgE levels or inhibiting NF-κB-mediated cellular proliferation in a mammal comprising compounds that are structurally similar to cited prior art references. Prior art references may have taught or suggested the compounds in the claimed composition, but they do not teach or suggest that a pharmaceutical composition can be made using structurally similar compounds. In fact, neither Masukawa nor Ninomiya suggests that the structurally similar compounds may have any biological or pharmaceutical activity. The situation here is distinguishable from *Dillon*. Since both prior art composition and claimed composition in *Dillon* were fuels with additives and the additives in both were structurally similar, the prior art teachings would have suggested using structurally similar compounds as fuel additive in the claimed composition. Here Masukawa and Ninomiya only teach including similar compounds in photographic and non-linear optical materials; therefore, have failed to teach or suggest a pharmaceutical composition for treating or preventing an allergic reaction associated with increased IgE levels or for inhibiting NF-κB-mediated cellular proliferation in a mammal. According, no *prima facie* obviousness can be found.

Even if mere structural similarity of compounds in the prior art and in Applicants' claimed compositions can create a presumption of obviousness, the presumption can be rebutted by the showing that claimed compositions possess unexpectedly improved properties or properties that the prior art does not have. *In re Dillon,* 919 F.2d 688, 692-3 (Fed. Cir. 1990). The prior art only teaches that the imidazole compounds can be used as cyan couplers and are excellent in spectral absorption, absorption coefficient and fastness. The present invention discloses the new properties of imidazole compounds, mainly for their ability to reduce or inhibit IgE responses and to inhibit NF-κB-mediated cellular proliferation, which were not even hinted in the prior art references. Furthermore, the subject matters of prior art disclosures involve the areas of photographic and non-linear optic materials and are so remote from the pharmaceutical science that the claimed biological/pharmaceutical activity cannot be obvious. A skilled person in the art would never expect or even guess that similar compounds would have presently claimed properties. Therefore, Applicants submit that the present pharmaceutical composition possess new properties not possessed by the prior art materials or suggested in the prior art. Accordingly, Applicants respectively request that the Examiner withdraw the objections under 35 U.S.C. §103(a).

Rejoinder

In the Amendment filed on March 1, 2006, an election was made without traverse to prosecute the invention of Group I, Claims 1-4 and 26. Accordingly, Group II, including Claims 5-14, which are directed to a method for treating or preventing allergic reaction and/or for inhibiting cytokines or leukocytes, Group III, including Claims 15-25, which are directed to a method for inhibiting cellular proliferation, and Group IV, including Claims 27-32, which are directed to a process of making, were withdrawn from consideration.

According to M.P.E.P. 821.04, where product and process claims drawn to independent and distinct inventions are presented in the same application, Applicant may be called upon under 35 U.S.C. §121 to elect claims to either the product of process. The claims to the non-elected invention will be withdrawn from further consideration under 37 C.F.R. §1.142. However, if Applicant elects claims directed to the product and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. Accordingly, Applicants respectfully request that upon allowance of Claim 1, the Examiner permit rejoinder of Claims 5-25 which depend from Claim 1 and Claims 27-32, which have been amended to depend from Claim 1, in accordance with M.P.E.P. 821.04. Thus, all of Claims 5-25 and 27-32 now depend from Claim 1 and recited all of the limitations of the allowed product claims.

CONCLUSIONS

In view of the remarks set forth above, Applicants respectfully submit that Claims 1-33 in this application are now in condition for allowance. Should there be any questions concerning this application, the Examiner is respectfully invited to contact the undersigned at telephone number appearing below. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 1/8/07

By: _____

Agnes Juang, Ph.D.
Registration No. 55,310
Attorney of Record
Customer No. 20,995
(949) 760-0404

3275591
010507